REMARKS

In view of the amendments and remarks that follow, Applicants respectfully submit that the application is in condition for allowance. Accordingly, applicants request reconsideration of the application, withdrawal of the objections and rejections of record and issuance of a Notice of Allowance.

Applicants would like to thank Examiner Russel for his time and courtesy during the personal interview on July 1, 2003. A Communication summarizing the interview is being submitted with this response.

Claims 1-32 and 35-39 are pending in the application. Claims 1-14, 30 and 35-39 are rejected and Claims 15-29, 31 and 32 are objected to for the reasons of record. Claims 30-32 have been cancelled and new claims 40-42 have been added to limit cancelled claims 30-32 based on the restriction requirement. Claims 1, 4, 5 and 15 have been amended in response to the various objections noted in Paper No. 14. The amendments and new claims are not considered to involve the addition of new matter and entry of the amended claims is respectfully requested.

A new substitute specification is being submitted herewith in order to correct the SEQ ID NOS to comply with the sequence rules. No new matter is contained within the substitute specification submitted with this response.

The disclosure was objected to because SEQ ID NOS were not inserted after every amino acid sequence in the application subject to the sequence disclosure rules as originally filed. The Examiner had required a substitute specification containing these additions, which is submitted herewith.

The substitute specification filed April 3, 2003 was not approved because it was not submitted with a statement of no new matter. A new substitute specification, as noted above, is submitted herewith along with the requisite statement of no new matter. Applicants submit that the new substitute specification is submitted in accordance with 37 CFR 1.121 (b) (3) and should be approved.

The listing of Claims beginning on page 3 of this paper is considered to replace the claims contained in the Substitute Specification submitted herewith.

A new Sequence Listing is being sent with this response in view of the changes made in the Substitute Specification. After careful review of the Sequence Rules, it was determined that a number of the prior sequences were not required and have subsequently been removed. Applicants request that the new Listing be carefully reviewed and that any informalities be communicated to Applicant as soon as possible.

Rejections Under 35 U.S.C. § 112, second paragraph

Claim 4-9 and 30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, in claim 4, the final R group is unclear because it contains bonds at both ends of the substituent. This is also found in Claims 5 and 30.

Applicants have amended each of these claims in order to overcome the 112, 2nd paragraph rejections. The final R group in Claims 4 and 5 has been removed and Claim 30 has been cancelled and replaced with new Claim 40 wherein this group has not been included. These amendments are considered to put these claims in condition for allowance.

Rejections Under 35 U.S.C. § 102(b), 102(e) and 35 U.S.C. § 103(a)

The examiner has noted that instant claims 1-32 and 35-39 are deemed not to be entitled under 35 U.S.C. § 119(e) to the benefit of the filing date of provisional application 60.189,387 because the provisional application, under 35 U.S.C. § 112, 1st paragraph, does not disclose, e.g., all of the E^{cp} groups recited in the instant claims. The examiner notes that Trouet et al., U.S. Patent No. 5,962, 216 is therefore available as prior art against the instant claims under 35 U.S.C. § 102(b).

Applicants respectfully disagree that the subject claims are not entitled to the benefit of the provisional filing date. However, in view of the following remarks, Trouet et al. is not considered to be relevant prior art against the instant claims.

Claims 1 and 2 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Trouet et al. The examiner notes that Trouet et al. teach the prodrug compound Gly-Leu-

Gly-Leu-DNR. This compound, the examiner notes, corresponds to Applicants' claimed compound in which E^{cp} is Cap-Gly-Xp1-Xp2-Laa where Cap is R, which is hydrogen.

Applicants respectfully traverse this ground of rejection and present the following comments. Nowhere in the specification or claims is R defined as hydrogen. Cap is defined as an N-terminus group selected from R-, Xa4 and R-Xa4. However, in order to expedite the prosecution of the application, a proviso has been added eliminating hydrogen as a capping group. This amendment of claim 1 is considered to overcome this ground of rejection.

In view of the foregoing, withdrawal of this ground of rejection is respectfully requested.

Claims 35-39 are rejected under 35 U.S.C. § 103 (a) as being obvious over Trouet et al. The examiner notes that the application of Trouet et al. is the same as in the 102(b) rejection of Claims 1 and 2. The examiner notes that while Trouet et al. does not teach administering the prodrug compound in combination with a pharmaceutically acceptable carrier in order to treat breast cancer/carcinoma, that it would be obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the prodrug of Trouet et al. to treat breast cancer/carcinoma. The examiner points out that it is desirable to treat such a disease and since Trouet et al. teaches that daunorubicin is released from its prodrug form by enzymes present in breast cancer/carcinoma cells, it would be obvious to one of ordinary skill in the art to administer the prodrug of Trouet et al. in combination with a pharmaceutically acceptable carrier since it is routine to administer therapeutic agent sin combination with pharmaceutically acceptable carriers for ease of storage, transportation, measurement and administration.

Applicants respectfully traverse this ground of rejection and provide the following comments. In view of the comments in response to the 102 (b) rejection, Applicants submit that since the compounds claimed in Claims 1 and 2 are novel, their use as claimed in Claims 35-39 would not be obvious over Trouet et al. Applicants submit that this ground of rejection should also be withdrawn.

Claims 1-14 are rejected under 35 U.S.C. § 103 (a) as being obvious over Trouet et as applied against Claims 1 and 2 above and further in view of WO Patent Application

00/64486. The examiner notes that Trouet et al. generally teach a terminal group W, especially succinyl, linked through a peptide Z to a therapeutic agent M, especially doxorubicin. The peptide Z is cleaved by enzymes secreted by the target cells to permit entry of the therapeutic agents into the target cells. Trouet et al., it is clearly noted by the examiner, do not teach a peptide Z which is cleavable by a matrix metalloproteinase and which corresponds to Applicants' elected E^{cp} group. The '486 application teaches an amino acid sequence Pro-Leu-Gly-Leu-Trp-Ala which is cleaved by matrix metalloproteinases. The examiner notes that the amino acid sequence of the '486 application corresponds to Applicants elected E^{cp} group as defined in instant Claims 1, 4, 5 and 10. The examiner concludes that it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the prodrugs of Trouet et al. using the amino acid sequence taught by the '486 application because Trouet et al's prodrugs can be formed using any peptide which is cleaved by an enzyme, and because the WO applications' amino acid sequence is described as being cleavable by an enzyme which is associated with the tumor cells which are to be treated by Trouet et al.

Applicants respectfully traverse the rejection and present the following comments. The elected E^{cp} group is Cap-Paa-Xa2-Gly-Xp1-Xp2-Laa-. The amino acid sequence taught in the '486 application does not correspond to Applicants' elected E^{cp} group. As argued above, R is not equal to H and as such takes the amino acid sequence taught in the '486 application outside the elected species. Additionally, claim 1 has been amended to specifically exclude succinyl as a substituent for Cap. Thus, without this crucial link, there is no basis for combining the references in order to render obvious the instant claims.

Applicants submit that the instant claims are not obvious over Trouet et al. in view of the WO 0064486 application and request that this ground of rejection be withdrawn.

Claims 1-5 and 35-39 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Monsigny et al. (U.S. Patent No. 4,703,107). The '107 patent, the examiner notes, teaches anti-tumoral prodrugs PHA-Gly-Gly-L-Arg-L-Leu-Daunorubicin and PHA Gly-Gly L-Arg-L-Leu-Adriamycin. The drugs are liberated from the prodrugs by proteases excreted from the tumoral cells. It is also noted that the prodrugs can be combined with pharmaceutically acceptable carriers. The examiner points out that the prodrugs

correspond to Applicants' claimed compound in which E^{cp} is Cap-Xa2-Gly-Xp1-Laa or Cap-Gly-Xp1-Xp2-Laa, where Cap is R, which is polyhydroxyalkanoyl.

Applicants respectfully traverse the rejection and present the following comments. Claim 1 has been amended to specifically exclude polyhydroxyalkanoyl as a Cap substituent. Support for this amendment is found in paragraph 0444 of the published specification. Clearly without this crucial piece, the '107patent cannot anticipate the instant claims. Applicants submit that this ground of rejection should be withdrawn.

Claims 1-14 and 35-39 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Firestone et al. (U.S. 2002/0147138 A1). The examiner notes that Firestone et al. teach the enzyme activated anti-tumor and anti-metastatic prodrug N-Cbz-Gly-Phe-Ala-Leu-doxorubicin. The peptide portion is noted to be capable of being cleaved by collagenase (IV) or elastase. The prodrug, the examiner states, corresponds to Applicants' claimed compounds in which E^{cp} is Cap-Gly-Xp1-Xp2-Laa. The examiner goes on to note that in view of the similarity in structure between the peptide portion of the prodrug of Firestone et al. and Applicants' claimed E^{cp} group, the prodrug of Firestone is deemed inherently to be cleavable by the matrixins specified in these claims. The examiner concludes that sufficient evidence of similarity is deemed to be present to shift the burden to Applicants to provide evidence that the claimed compounds are unobviously different than that of Firestone et al.

Applicants respectfully traverse the application and present the following comments. The examiner notes that Firestone et al. teach a particular prodrug containing N-Cbz as the amino protecting group. Claim 1 has been amended to delete N-Cbz from the definition of "Cap". This amendment is considered to overcome the rejection over Firestone and Applicants submit that the rejection under 35 U.S.C. § 102 (e) over Firestone et al. should be withdrawn.

Applicants acknowledge the examiner's comments that Claims 15-29 would be allowable if rewritten to overcome the claim objections set forth in the action and to include all of the limitations of the base claim and any intervening claims.

The examiner has also noted that Claim 30 limited to the elected SEQ ID NO would be allowable if rewritten to overcome the rejections under 35 U.S.C. § 112, 2nd paragraph,

and to include all of the limitations of the base claim and any intervening claims. Claims 31-32 are objected to a being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. It is acknowledged that the prior art of record does not teach or suggest an E^{cp} group having the structure of the elected SEQ ID NO.

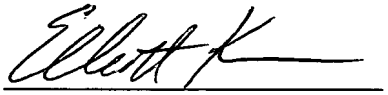
Claims 30-32 have been each cancelled and replaced with new claims 40-42 which are limited to the elected SEQ ID NO. These claims are considered to address the Examiner's comments and to put the application in condition for allowance.

In view of the foregoing, Applicants submit that the application, as amended, is in condition for allowance and courteously solicit a Notice of Allowance.

If any fee due is not accounted for herein, please charge such fee to Deposit Account No. 19-3880. If any extension of time is required and not petitioned for, such extension is hereby petitioned for, and it is requested that any fee due in connection therewith be charged to the aforementioned Deposit Account.

The foregoing amendment and response are believed to be fully responsive to the outstanding Office Action. If a direct personal communication would advance the prosecution of this application, please contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,



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